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● *Original Contribution*

INVESTIGATING THE EFFECT OF THERMAL STRESS ON NERVE ACTION POTENTIAL USING THE SOLITON MODEL

Mojtaba Haji Hasani,* Shahriar Gharibzadeh,* Yaghoub Farjami,† and Jahan Tavakkoli‡
*Department of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran; †Department of Computer Engineering, Qom University, Qom, Iran; and ‡Department of Physics, Ryerson University, Toronto, ON, Canada

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Abstract—The thermal mechanism of acoustic modulation of the reversible electrical activities of peripheral nerves is investigated using the soliton model, and a numerical solution is presented for its non-homogenous version. Our results indicate that heating a small segment of the nerve will increase the action potential conduction velocity and decrease its amplitude. Moreover, cooling the nerve will have the reverse effects, and cooling to temperatures below the nerve melting point can reflect back a significant portion of the action potentials. These results are consistent with the theory of the soliton model, as well as with the experimental findings. Although there exists a discrepancy between the results of the soliton model and experimental pulse amplitude data, from the free energy point of view, the experiments are compatible with Heimburg and Jackson theory. We conclude that the presented model accompanied by the free energy view is capable of simulating the effects of thermal energy on nerve function. One potential application of the developed theoretical model will be investigation of the reversible and irreversible effects of thermal energy induced by various energy modalities, including therapeutic ultrasound, on nerve function. (E-mail: gharibzadeh@aut.ac.ir) © **2015 Published by Elsevier Inc. on behalf of World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Nerve heating, Soliton model, Action potential, Numerical solution, Gibbs free energy.**

INTRODUCTION

Studies of the effects of ultrasound (US) on the nervous system started in the early 20th century. Moreover, the mechanisms underlying US bio-effects on nerves, especially at low power, are not fully understood, and to date, there is no established theory explaining these effects. In recent years, quite a few researchers have considered therapeutic applications of US to both the central (Bystritsky et al. 2011) and peripheral (PNS) (Muratore and Vaitekunas 2012) nervous systems. The PNS, which is the subject of this article, includes neurons containing receptors that are attached to long axons transferring action potentials (APs) to the other end of the cells. Because ultrasound of a small segment of the axon can modulate its electrical activities, understanding the mechanism in the region of interest, rather than in synapses and receptors, is the main focus of the current research. Recently, Muratore and Vaitekunas (2012) summarized the response of the electrical activity of PNS to ultrasonic exposure. They characterized three stages in terms of US energy deposition: (i) When the US energy delivered to a nerve is larger than a specified threshold, nerve activity will be accelerated. The interaction at this stage is attributed to the non-thermal effect of US (Farmer 1968; Mihran et al. 1990, 1996; Ochs et al. 2000; Schelling et al. 1994; Tsui et al. 2005). Increasing the ultrasonic energy results in the return of nerve activity to normal (*i.e.*, the level before insonification), resulting in the misconception that there was no effect. The relative role of each US bio-effect, including thermal and non-thermal bio-effects, in this regime has not yet been determined. (ii) After passing this ill-defined threshold, the PNS exhibits reversible depression, which is due mostly to the thermal effect (Colucci et al. 2009; Currier and Nelson 1969; Halle et al. 1981; Jabbary 2011; Kramer 1985; Kramer and Currier 1982; Lele 1963; Moore et al. 2000; Tsui et al. 2005). (iii) At very high ultrasonic energies, the modality is converted to coagulative therapy, which has irreversible effects on action potentials (Foley et al. 2007, 2008; Jabbary 2011). The aim of the work described here was to develop a new theoretical model to investigate the thermal mechanism underlying reversible acoustic modulation of PNS nerve activity.

Address correspondence to: Shahriar Gharibzadeh, Neuromuscular Systems Lab, Faculty of Biomedical Engineering, Amirkabir University of Technology, 424 Hafez Ave, Tehran, Iran. E-mail: gharibzadeh@aut.ac.ir

The excitability modifications resulting from radiation forces are attributed to mechanical changes in the function of the voltage-gated ion channels, which are involved in generating action potentials (APs) (Mihran et al. 1996; Tyler et al. 2008). In fact, it has been found that voltage-gated ion channels are sensitive to stress and strain applied to the axon's membrane. Moreover, there are distinct stretch-activated ion channels in axons (Sachs 2010; Schmidt et al. 2012). On the other hand, it has been reported that the rate of activation/inactivation of voltage-gated ion channels is a function of temperature rise, which in turn accelerates nerve repolarization to levels higher than the normal state (Colucci et al. 2009). To date, most researchers have attempted to explain the mechanism of nerve activity modulation on the basis of the Hodgkin–Huxley (HH) theory. This theory hypothesizes that the complex structural proteins in the membrane act like ion-selective channels, which are sensitive to voltage (Hodgkin and Huxley 1952). In contrast, discrete ion conduction events have been recorded on synthetic and pure lipid membranes close to the chain melting transition temperature that resemble ion conductance through protein channels to a degree that is fairly indistinguishable (Heimburg 2010; Laub et al. 2012; Yafuso et al. 1974). Heimburg (2010) introduced the theory of lipid ion channels and claimed that their occurrence depends on temperature, lateral tension, membrane-associated drugs such as anesthetics and neurotransmitters, pH, calcium concentration, voltage and other thermodynamic variables. Therefore, the role of both peripheral and integral proteins devolves into adjusting and influencing the chain melting point and may change the likelihood of lipid channel formation (Heimburg and Jackson 2005).

Previous studies have reported that mechanical change in the thickness of nerve axons, as well as reversible heat production in nerve membranes, would be simultaneously propagated with the voltage AP (Abbott et al. 1958; Iwasa et al. 1980). This adiabatic process is strikingly contradictory to HH theory, according to which irreversible heat is produced and dissipated into the environment (Andersen et al. 2009). Moreover, melting transition temperatures of many biological membranes are slightly below body temperature where non-linear behavior has been observed in heat capacity, volume and area compressibilities and relaxation times. Heimburg and Jackson (2005) have proposed that under these conditions, together with the existence of dispersion in the nerve membranes, the generation and propagation of electromechanical solitons along membrane cylinders could be expected. In this theory, the change in local density of the membrane is similar to the propagation of a piezo-electric wave (Jackson and Heimburg 2007). They introduced a thermodynamic model in which nerve pulses are described as a localized density excitation that propagates in the axon membrane without any distortion (Heimburg and Jackson 2005). Indeed, the soliton model is derived by adding a fourth-order derivative term which represents dispersion in the sound wave equation for compressible fluids. Lautrup et al. (2011) numerically solved the current form of the soliton equation to investigate the stability of solitons when confronted by small-amplitude fluctuations and dissipation. However, based on the soliton model, nerve pulses pass through each other and preserve their shape with only minor loss of energy, whereas APs are physiologically blocked as a result of such collisions (Lautrup et al. 2011; Tasaki 1949). As a numerical solution, Lautrup et al. rewrote the soliton equation as two first-order equations. In-depth investigation of the non-homogeneous version of the soliton equation and an appropriate numerical method to solve it are the main objectives of our study.

To improve our understanding of the mechanisms responsible for the modulation of nerve activities by insonification-induced heat, a comprehensive model of nerve pulse is a proper alternative to existing methods. To this end, Heimburg–Jackson (HJ) theory is considered to be the optimal method.

Next, a short description of the current form of the soliton equation is given, followed by derivation of the novel non-homogeneous version of the soliton equation. A numerical approach based on a Numerov-type method is described (Chawla and Rao 1987). The temperature changes in our model are then interpreted. Experiments performed to determine the influence of both rising (heating) and falling (cooling) temperatures and the size of the heated region are described. Finally, the correlation between our soliton model results and the free energy results of HJ theory are discussed and compared with experimental outcomes.

METHODS

Soliton model

The soliton model of Heimburg and Jackson (2005) is derived from the simple wave equation for sound propagation in one dimension. The assumption is that the nerve axon is an infinitely long and narrow (1-D) cylinder with a specific lateral density (density in 2-D surfaces) on which excitations move along the long axis, z.

Some theoretical and experimental studies indicate that for a surface area (A), isentropic compressibility (K_S^A) is equal to isothermal compressibility (K_T^A), $K_S^A = K_T^A$, although in high-frequency waves (*i.e.*, frequencies above a few megahertz), some discrepancy was observed. Accordingly, the model needs a term that represents the dispersion effect. Moreover, for low-amplitude